

SHORT REVIEW

on a dissertation for awarding the educational and scientific degree

"Doctor" in 7.1 Medicine (03.01.50) "Pediatrics"

Author of the dissertation: Dr. Kalin Yordanov Lisichki, PhD student of independent training at the Department of "Internal Diseases, Pharmacology and Clinical Pharmacology, Pediatrics, Epidemiology, Infectious and Skin Diseases", Faculty of Medicine, SU "St. Kliment Ohridski"

Topic: "Macrophage Activation Syndrome in childhood - analysis of clinical-laboratory control and laboratory changes, evaluation of the diagnostic approach and therapeutic effectiveness"

Area of higher education: 7. Health care and sports; *Professional field:* 7.1 Medicine; *Scientific specialty:* (03.01.50) "Pediatrics"

Scientific supervisors: Prof. Dr. Stefan Nedev Stefanov, PhD and Assoc. Prof. Dr. Yordanka Georgieva Uzunova, PhD

Author of the short review: Prof. Tsvetanka Tsankova Marinova, MD, PhD, DMSc, Faculty of Medicine of Sofia University "St. Kliment Ohridski" (Order for composition of the Scientific Jury of the Rector of SU No. RD-38-297/21.06.2022)

PhD student's curriculum vitae and academic development

Dr. Kalin Yordanov Lisichki was born on 11.10.1958. He is a graduate of the Higher Medical Institute - Sofia at the Medical Academy (1978-1984). Dr. Lisichki holds diplomas for completed higher education in the specialty of *Medicine* (Reg. No. 32985/12.09.1984) and for acquired specialties in *Pediatrics* (1991) and in *Pediatric Rheumatology* (1997). From 1987 to 2007, he worked as an assistant and chief assistant at the University Children's Hospital – Sofia. Since 2007 and up to the present moment, he has worked as a doctor and Head of the Pediatric Clinic (since 2013) at UGHAT "Tokuda".

In 2021, Dr. Kalin Lisichki was enrolled as a PhD student of independent training

for obtaining the educational and scientific degree "Doctor" in the Department of "Internal Diseases, Pharmacology and Clinical Pharmacology, Pediatrics, Epidemiology, Infectious and Skin Diseases", Faculty of Medicine, SU "St. Kliment Ohridski" in professional field 7.1. Medicine, scientific specialty (03.01.50) "Pediatrics" by order No. RD-20-1713/15.09.2021 of the Rector of SU "St. Kliment Ohridski".

Data for the dissertation

Characteristics of the structure of the dissertation work

The dissertation is written on 123 standard pages and includes: Introduction; Literature review; Purpose and tasks; Materials and methods; Results; Discussion; Conclusions; Contributions; Literature. It is illustrated with 37 figures and 8 tables. In the bibliographic list, 203 literary sources are cited, of which 2 are in Cyrillic and 201 are in Latin. The volume of the individual parts of the dissertation is well balanced.

Relevance and significance of the dissertation work

The dissertation is an up-to-date, in-depth and unquestionably contributing research. It analyzes the *Macrophage Activation Syndrome (MAS)* in childhood as a complex of specific pathological changes, including a hyperinflammatory response of the body to various stimuli with the participation of immunocompetent cells (mainly macrophages, CD8+ T-lymphocytes, and NK-cells), their receptors and cytokines (mostly IL-1, IL-6, IL-18, TNF α , and γ IFN). In the dissertation, an in-depth analysis of the clinical characteristics, laboratory parameters and therapeutic approaches in children with MAS was made.

New data have been obtained from the PhD student regarding the pathogenesis of MAS, the difficulties of its diagnosis and treatment. The possibilities for the development of hemophagocytic lymphohistiocytosis in some autoimmune, malignant and infectious diseases are discussed. The dissertation work has a very significant theoretical and scientific-applied value for pediatrics, immunology and cell biology.

Characterization and evaluation of the content of the dissertation work

The introduction includes a thorough analysis of literature data and original ideas about the pathogenesis, diagnostic markers, symptoms and therapy of MAS.

The literature review is comprehensive (30 pages) and analytical. It is proof of Dr. Lisichki's excellent knowledge of the subject of the dissertation. The review conscientiously discusses the available literature on MAS and the rationale for its study.

The author's conclusion is that MAS occurs in both children and adults, is often severe and often fatal. The absence of categorical clinical signs, characteristic laboratory changes and a generally accepted therapeutic scheme for application in MAS are grounds for the doctoral student to formulate the goal and tasks of his study.

The aim of the dissertation is to make a complex characterization of MAS through a more detailed description of childhood patients diagnosed with MAS in Bulgaria; to analyze established clinical and laboratory changes; and to evaluate the applied diagnostic approach and the effect of the carried out treatment.

The research tasks are eight. They have been correctly edited and successfully implemented by the PhD student: Distribution by gender and age; An attempt should be made to establish the triggers of the underlying disease; To present the clinical characteristics of the syndrome; To examine in detail and evaluate changes in laboratory parameters in the MAS; To analyze the effect of the administered medications to control the clinical changes in the MAS; To analyze the effect of administered medications on changes in laboratory parameters; To give a proposal for an up-to-date diagnostic approach; To give a suggestion for an effective therapeutic strategy.

Materials and methods

The section is presented on 6 pages and includes data analysis for 20 children with MAS and a control group of children. They were diagnosed, treated and followed up in a total of four hospitals (in the cities of Sofia, Plovdiv and Varna) for the period from 2013 to 2019.

The indicators that are the subject of analysis are divided into four groups with subgroups, including: 1. Distribution by gender and age; 2. Distribution according to triggers of MAS; 3. Evaluation of the clinical symptoms of MAS; 4. Evaluation of paraclinical indicators, including: Clinical laboratory indicators (Hematological indicators, Markers of inflammation, and Biochemical indicators and others);

Microbiological tests; Immunological tests; Genetic analysis; Imaging methods; Bone marrow puncture with evaluation for hemophagocytosis; and Statistical analysis.

In all patients, the diagnosis of MAS was accepted according to the current diagnostic criteria for this disease of PRINTO/EULAR from 2016.

The methodological approach of the PhD student is complex and adequate to the set goal. The fact that Dr. Lisichki independently and very competently uses diverse and time-consuming research methods deserves attention.

Results

The obtained results (from page 45 to 85) are presented in five sections with the following sequence: 1. Distribution by gender, age, triggers and clinical symptoms of macrophage activation syndrome; 2. Presentation of results of laboratory tests (Analysis of results of indicators of inflammatory activity and some parameters of a complete blood count, which are related to MAS; Analysis of results of research of biochemical indicators; and Bone marrow puncture); 3. Presentation of the results of the data processing for the carried out treatment (Treatment with a corticosteroid in a high-dose regimen and cyclosporine; Treatment of MAS with biological agents – anakinra); 4. Comparative evaluation of serum ferritin values in MAS and in other diseases with high inflammatory activity; 5. Evaluation of the change in the values of the laboratory parameters that are included in the diagnostic criteria for MAS.

The description of the own results is thorough and comprehensive. It proves the excellent methodical and clinical training of Dr. Lisichki, his diligence, conscientiousness and precision in his work. The results are presented in a logical sequence and very competently.

The obtained data are interesting and significant in fundamental and scientific-applied terms. They have applied importance both in medical practice and also in the field of immunology and cell biology.

In their entirety, the obtained results are a significant contribution to the extremely scarce literature data on pediatric patients with MAS in Bulgaria.

The discussion (from page 86 to 101) of the presented results includes well organized information on the essential characteristics of MAS, studied with regards to its clinical, paraclinical and therapeutic aspects.

The author's style testifies to his ability to compare literary data, skillfully analyze the obtained results and make motivated generalizations.

The illustrative material is sufficient in volume to fulfill the tasks of the dissertation work. The attached 37 figures and 8 tables are very competently prepared and interpreted. They convincingly support the presented data.

The formulated conclusions are 16 and reflect the obtained results very correctly.

The contributions of the dissertation are three groups: Contributions of an original nature (six); Contributions of an applied nature (two) and Contributions of a confirmatory nature (three).

The dissertation describes and summarizes data on children diagnosed with MAS in Bulgaria for the first time. Therapeutic regimens used to treat MAS in childhood have been thoroughly analyzed. Evidence is presented for the positive effect of the application of biological therapy (for example with anti-IL-1-receptor antagonists), allowing the clinical-laboratory control of MAS.

Publications and scientific communications thematically related to the dissertation work

Dr. Kalin Lisicki is the author of 6 scientific publications in refereed and indexed journals (4 national and 2 foreign ones, in five of which he is the first author) and 4 scientific communications (reported by him at scientific congresses and conferences).

The abstract was prepared in accordance with the regulatory requirements. It faithfully reflects the most significant results and scientific contributions of the dissertation work.

Dr. Kalin Lisichki is a hardworking, responsible, well-intentioned and tolerant colleague. He has a lot of professional experience in organizing and implementing all major types of pediatric, administrative and educational activities, shows very good communication skills and the ability to work in a team.

Conclusion

The dissertation presented for review is an up-to-date in design and methodically well-crafted clinical study, the result of painstaking and precisely executed research work. The results obtained are appropriately presented, well documented, competently discussed, and have an original contribution to the fields of pediatrics, immunology, and cell biology.

In terms of volume and quality, the dissertation work fully meets the requirements of the Law on Development of Academic Staff in the Republic of Bulgaria (LDASRB) and the Regulations for its application with regards to awarding the educational and scientific degree "Doctor".

In conclusion, the significance and significant scientific and applied value of the peer-reviewed dissertation "Macrophage Activation Syndrome in childhood - analysis of clinical-laboratory control and laboratory changes, evaluation of the diagnostic approach and therapeutic effectiveness" give me reason to evaluate it positively and fully convinced to offer to the respected members of the Scientific Jury to award its author Dr. Kalin Yordanov Lisichki the educational and scientific degree "Doctor" in Scientific specialty: 7.1. Medicine (03.01.50) "Pediatrics".

08. 08. 2022

Sofia

A member of the Scientific Jury:

(Prof. Ts. Marinova, MD, PhD, DMSc)